Original Article

PI PROSTATE INTERNATIONAL

Prostate Int 2014;2(4):169-175 • http://dx.doi.org/10.12954/PI.14057

The role of 3-tesla diffusion-weighted magnetic resonance imaging in selecting prostate cancer patients for active surveillance

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Purpose: Differentiating significant cancer from insignificant cancer is a major challenge in active surveillance (AS) for prostate cancer. We evaluated whether the apparent diffusion coefficient (ADC) grade from 3-T diffusion-weighted magnetic resonance imaging (DW-MRI) is useful to exclude men with unfavorable pathological features from men meeting current AS eligibility criteria.

Methods: Among patients who underwent radical prostatectomy, 117 potential AS candidates defined according to 2013 European Association of Urology guidelines who had undergone preoperative 3-T DW-MRI were included. A blinded uro-radiologist graded the level of suspicion from the ADC map using the Likert scale from 1 to 5. The rate of unfavorable pathological features was evaluated according to ADC grade. Unfavorable pathological features were defined as non–organ-confined disease or pathological Gleason score ≥ 7 (4+3). The associations between unfavorable pathological features and clinical variables including ADC grade (> 3 vs. ≤ 3) were evaluated using logistic regression analysis.

Results: The rates of unfavorable pathological features were 0.0% (0/14), 2.9% (1/34), 5.4% (2/37), 25.0% (6/24), and 37.5% (3/8) from grades 1 to 5 ($P = 0.002$). The predictive accuracy was as high as 0.804. The rates were significantly different between low (≤ 3, 3.5%) and high (> 3, 28.1%, $P < 0.001$) grades. The sensitivity, specificity, and positive and negative predictive values were 75.0%, 78.1%, 28.1%, and 96.5%. ADC grade (odds ratio [OR], 10.696; 95% confidence interval [CI], 2.675–42.773) was significantly associated with unfavorable pathological features, even after adjusting for other variables (OR, 11.274; 95% CI, 2.622–48.471).

Conclusions: ADC grade from 3-T DW-MRI is useful to predict men with unfavorable pathologic features from AS candidates.

Keywords: Prostatic neoplasms, Watchful waiting, Pathology, Magnetic resonance imaging

INTRODUCTION

The chief treatment for localized prostate cancer (PC), even very low-risk disease, remains radical prostatectomy (RP) [1,2]. However, autopsy studies have demonstrated that 60%–70% of elderly men have histological PC [3], although only one-third of them are clinically diagnosed before death [4]. Furthermore, from 2.3% to 25% of unselected PC cases may have insignificant pathological features after surgery [5]. Thus, overtreatment is currently a major concern for low-risk localized PC. Publication of the PIVOT trial in particular, has amplified this issue, because RP did not significantly improve overall or disease specific survival compared with observation in the PIVOT trial [6].

Active surveillance (AS) is an attempt to reduce such overtreatment. Early series of AS demonstrated excellent cancer-

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Submitted: 18 June 2014 / Accepted after revision: 1 October 2014

specific and overall survival; however, one-third of patients required definitive treatment during a median 80 months or shorter follow-ups [2,7]. Thus, around one-third of patients might not be offered appropriate treatment at the proper time. Furthermore, longer-term oncological outcomes and quality of life are still unclear. Thus, the major challenge of differentiating those men who have significant cancer from those with insignificant cancer remains unresolved.

Recent reports suggest an emerging role for multiparametric magnetic resonance imaging (MRI) in PC diagnosis [8]. In particular, diffusion-weighted (DW)-MRI has been the focus of interest for its ability to identify aggressive cancer with higher Gleason score [9-12]. However, little is known regarding the role of DW-MRI in selecting PC patients for AS. Thus, we evaluated whether the apparent diffusion coefficient (ADC) grade determined with 3-T DW-MRI is useful for excluding men with unfavorable pathological features from current AS candidates.

MATERIALS AND METHODS

1. Ethics statement

This study was approved by the Institutional Review Board (IRB) of Seoul National University Bundang Hospital (Seongnam, Republic of Korea). The approval number is B-1307/212-109.

2. Patients

We retrospectively reviewed the patients who underwent RP from January 2008 through April 2013 in Seoul National University Bundang Hospital. The eligibility criteria were AS candidates defined according to 2013 European Association of Urology guidelines (clinical stage T1c-T2a, prostate-specific antigen [PSA] ≤ 10 ng/mL, biopsy Gleason score ≤ 6 [at least 10 cores], ≤ 2 positive cores, ≤ 50% cancer involvement in each core) [2], who had undergone preoperative 3-T multiparametric prostate MRI at our institution. We conducted multiparametric prostate MRI as a routine preoperative evaluation for RP. Almost all patients underwent either 1.5-T or 3-T MRI, and selection of magnetic field strength was determined not by clinical parameters but by schedule of the test. Men who had undergone any kind of neoadjuvant treatment or prior prostate surgery were excluded, because these interventions could affect the MRI reading and pathological outcome.

Among 1,377 men treated with RP during the study period, 25 and 14 patients were excluded because of neoadjuvant therapy and prior prostate surgery, respectively, and 237 patients met AS candidate eligibility according to the above definition. Of these, 117 patients underwent 3-T multiparametric prostate MRI and were included in the final analysis.

3. MRI protocol and ADC grading

All MRI examinations were performed after biopsy, usually 2 to 6 weeks later. MR images were taken using a 3.0-T MR system (Intera Achieva 3.0T, Philips Medical Systems, Best, The Netherlands) equipped with a phased-array cardiac 6-channel coil. In accordance with the recent guideline for prostate MR [13], we did not use an endorectal coil. All patients were injected with 20 mg butylscopolamine (Buscopan, Boehringer Ingelheim Pharma, Ingelheim, Germany) intramuscularly to suppress bowel peristalsis 30 minutes before imaging. Axial DW images were acquired using single-shot echo planar imaging. Scan parameters were as follows: TR, 2,500–3,000 ms; TE, 56–65 ms; slice thickness, 3 mm; interslice gap, 1 mm; field of view, 180 mm × 180 mm; matrix, 92 × 90; and number of excitations, 10. Diffusion encoding gradients were applied as a bipolar pair at b-values 0 and 1,000 s/mm^2. ADC maps were automatically generated on a pixel-by-pixel basis.

An experienced uro-radiologist (S.I.H.), who was blinded to all clinical variables including pathological outcome, independently graded the level of suspicion for clinically significant cancer from ADC mapping images using the Likert scale from 1 to 5 as follows: grade 1, highly unlikely to be present; grade 2, unlikely to be present; grade 3, equivocal; grade 4, likely to be present; and grade 5, highly likely to be present

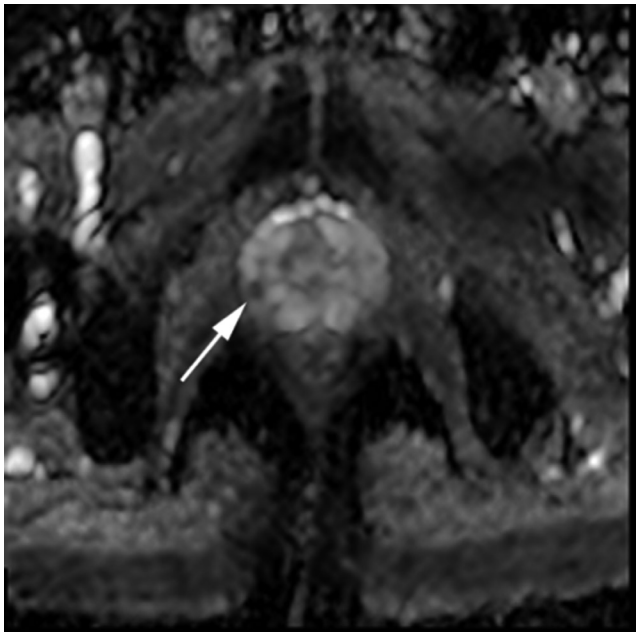

Fig. 1. Axial apparent diffusion coefficient map shows focal low signal intensity nodule (arrow) at right peripheral zone, which was graded 5.

http://dx.doi.org/10.12954/PI.14057

(Fig. 1) [14]. No T1 or T2-weighted images were used for grading the level of suspicion.

4. Outcome measurements and statistical analysis

Several key pathological features were evaluated according to the ADC grade. The evaluated outcomes included extraprostatic extension, seminal vesicle invasion, lymph node metastasis, positive surgical margin, pathological Gleason score ≥ 7 (any score combination), pathological Gleason score ≥ 7 (4+3), tumor volume < 0.5 mL, insignificant cancer, and unfavorable pathological features. Insignificant cancer was defined by the Stamey criteria (organ-confined, Gleason score ≤ 6, and tumor volume < 0.5 mL) [5]. Unfavorable pathological features were defined as nonorgan confined disease or pathological Gleason score ≥ 7 (4+3) regardless with surgical margin status. We focused our analysis to evaluate the association between ADC grade and unfavorable pathological features. The predictive accuracy for unfavorable pathological features was assessed using the area under the receiver operating characteristic curve (AUC). After dividing the low- (≤ 3) and high-grade (> 3) cases, the rates of unfavorable pathological features were compared. To evaluate the diagnostic value, we also calculated sensitivity, specificity, and positive and negative predictive values.

The associations between the unfavorable pathological features and clinical stage (T2a vs. T1c), PSA level, PSA density (≥ 0.15 vs. < 0.15), positive core number (2 vs. 1), maximal percentage of cancer involvement in cores, and ADC grade (> 3 vs. ≤ 3) were evaluated using logistic regression analysis. To adjust for other significant variables, we constructed a multivariate logistic regression model using ADC grade (> 3 vs. ≤ 3) and the other significant variables by univariate logistic regression analysis. To evaluate the additive effect of ADC grade on other variables, we also constructed a multivariable logistic regression model without ADC grade (> 3 vs. ≤ 3) and then compared the 2 AUCs.

The data are expressed as the mean ± standard deviation of the mean. If needed, the range of values is also presented. *P* values of < 0.05 were considered to be statistically significant.

Table 1. Basic characteristics of the patients

Characteristic	Value
Age (yr)	65.3 ± 6.4 (43–76)
Clinical stage	
cT1	94 (80.3)
cT2a	23 (19.7)
PSA (ng/mL)	5.5 ± 2.0 (1.7–9.9)
PSA density (ng/mL/mL)	0.15 ± 0.06 (0.05–0.46)
PSA density	
< 0.15	68 (58.1)
≥ 0.15	49 (41.9)
Positive biopsy cores	
1	81 (69.2)
2	36 (30.8)
Maximum % of core	14.9 ± 10.3 (1.3–46.7)

Values are presented as mean ± standard deviation (range) or number (%).
PSA, prostate-specific antigen.

RESULTS

The basic characteristics of the 117 patients are shown in Table 1. No seminal vesicle invasion or lymph node metastasis occurred in the cohort. Other key pathological outcomes according to ADC grade are summarized in Table 2. Extraprostatic extension, positive surgical margin, and unfavorable pathological features significantly differed between grades. However, no insignificant cancer was observed in ADC grade-5 patients, and no unfavorable pathological features were observed in ADC grade-1 patients.

The predictive accuracy measured by AUC was as high as 0.804 (95% confidence interval [CI], 0.680–0.928) (Fig. 2). The rate of unfavorable pathological features significantly differed between low (≤ 3) and high (> 3) grades (3.5% vs. 28.1%, $P < 0.001$). With this cutoff point (> 3) for grade, the sensitivity, specificity, and positive and negative predictive values were 75.0%, 78.1%, 28.1%, and 96.5%, respectively.

Table 2. Key pathological outcomes after radical prostatectomy according to ADC grade

ADC grade	Extraprostatic extension	Positive surgical margin	Pathologic Gleason ≥ 7	Pathologic Gleason ≥ 7 (4+3)	Tumor volume < 0.5 mL	Insignificant cancer	Unfavorable pathologic features
1 (n = 14, 12.0%)	0 (0)	0 (0)	7 (50.0)	0 (0)	2 (14.3)	2 (14.3)	0 (0)
2 (n = 34, 29.1%)	1 (2.9)	1 (2.9)	21 (61.8)	0 (0)	6 (17.6)	4 (11.8)	1 (2.9)
3 (n = 37, 31.6%)	1 (2.7)	2 (5.4)	20 (54.1)	1 (2.7)	10 (27.0)	8 (21.6)	2 (5.4)
4 (n = 24, 20.5%)	4 (16.7)	3 (12.5)	16 (66.7)	2 (8.3)	6 (25.0)	4 (16.7)	6 (25.0)
5 (n = 8, 6.8%)	3 (37.5)	4 (50.0)	7 (87.5)	1 (12.5)	1 (12.5)	0 (0)	3 (37.5)
P-value	0.003	< 0.001	0.387	0.239	0.742	0.567	0.002

Values are presented as number (%).
ADC, apparent diffusion coefficient.

Positive core number (2 vs. 1, $P=0.038$), maximal percentage of cancer involvement in cores ($P=0.024$), and ADC grade (>3 vs. ≤ 3, $P=0.001$) were significantly associated with unfavorable pathological features by univariate logistic regression analyses (Table 3). Multivariate logistic regression models with or without ADC grade are shown in Table 3. After adjusting for other variables, ADC grade was still a significant predictor (odds ratio [OR], 11.274; 95% CI, 2.622–48.471, $P=0.001$). Adding ADC grade led to an increase in AUC of 0.130 compared with the multivariate logistic regression model without ADC grade (0.861 vs. 0.731).

DISCUSSION

DW-MRI is a form of functional MRI derived from the movement of hydrogen protons in water molecules. The ADC is calculated by the distance of the movements, thus it is reversely correlated with tissue cellularity. Higher grade PC usually has higher cellularity and decreased extracellular space. Therefore, ADC is decreased in cancerous tissue in the prostate [8]. The value of the ADC lies not only in its localization of PC but also its correlation with cancer aggressiveness [9]. Tumors with lower ADC values have been revealed as having larger tumor volume and higher Gleason score [11,12,15,16]. Based on these advantages, the clinical value of DW-MRI stands out among multiparametric MRI protocols. Many researchers are exploring its clinical implications for AS.

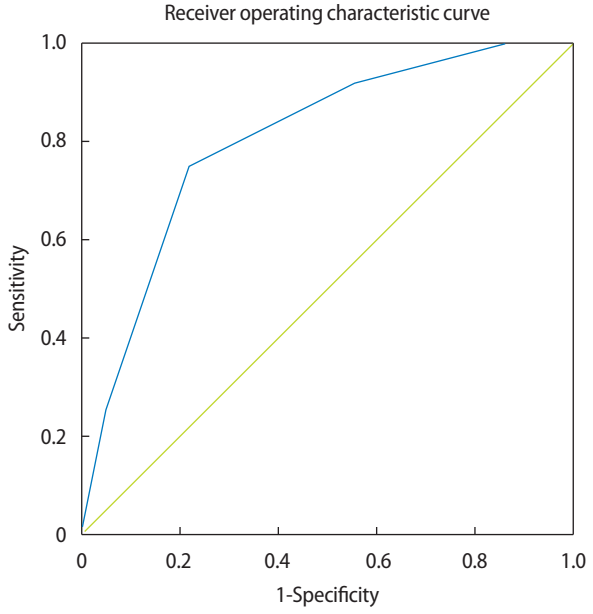

Fig. 2. The receiver operating characteristic curve of apparent diffusion coefficient grade predicting unfavorable pathologic features. The area under the curve was 0.804 (95% confidence interval, 0.680–0.928).

In the Royal Marsden AS cohort, among 86 men who underwent 1.5-T multiparametric MRI, tumorous ADC was significantly associated with both adverse repeat biopsy results (hazard ratio [HR], 1.3; 95% CI, 1.1–1.6) and time to definitive intervention (HR, 1.5; 95% CI, 1.2–1.8) [10]. These findings were confirmed by their similar prospective study [17]. The MR-PRIAS Collaboration Group performed a correlation study of RP specimens with a small number of patients (n=23) [9]. The participants were not AS candidates, but had biopsy Gleason scores≤6. The authors concluded that 3-T DW-MRI could predict the presence of tumor components with Gleason score≥4 in the final pathology assessment. Subsequently, they conducted a nested study within PRIAS, a prospective large-scale AS study [18]. They performed MRI-guided biopsy using 3-T multiparametric MRI at the time of AS inclusion to re-stratify risk. Tumors with a higher Gleason score (>6) had significantly lower ADC values than those with lower Gleason score (≤6).

Other trials using combinations of several multiparametric MRI protocols to select AS candidates have also been performed. Most of them were tested in RP series of low-risk patients or at the time of AS inclusion with confirmatory biopsy [19-21]. However, this approach may not be widely applicable in daily practice.

Table 3. Logistic regression analyses predicting unfavorable pathologic features

Variable	Univariate analyses		Multivariate model 1		Multivariate model 2	
	Odds ratio (95% CI)	*P*-value	Odds ratio (95% CI)	*P*-value	Odds ratio (95% CI)	*P*-value
Clinical stage, T2a vs. T1c	0.800 (0.163–3.930)	0.783	-	-	-	-
PSA (ng/mL)	0.950 (0.702–1.286)	0.740	-	-	-	-
PSA density, ≥0.15 vs. <0.15	2.100 (0.625–7.058)	0.230	-	-	-	-
Positive number cores, 2 vs. 1	3.669 (1.078–12.487)	0.038	2.597 (0.704–9.576)	0.152	3.328 (0.761–14.544)	0.110
Maximum % of cancer involvement in cores	1.062 (1.008–1.119)	0.024	1.048 (0.991–1.108)	0.099	1.036 (0.973–1.102)	0.270
ADC grade, >3 vs. ≤3	10.696 (2.675–42.773)	0.001	-	-	11.274 (2.622–48.471)	0.001
AUC (95% CI)	-	-	0.731 (0.641–0.808)	-	0.861 (0.785–0.918)	-
AUC difference	-	-	Reference	-	0.130	-

CI, confidence interval; PSA, prostate-specific antigen; ADC, apparent diffusion coefficient.

http://dx.doi.org/10.12954/PI.14057

Our present investigation was a correlation study between ADC grade and RP pathology in men who met AS eligibility. To our knowledge, this report is the first comprehensive pathological analysis of the value of ADC grade generated from 3-T DW-MRI in AS candidates. Higher resolution can be obtained with 3-T compared to 1.5-T MRI not only for conventional images but also for ADC maps due to its higher signal-to-noise ratio [13]. Transition from 1.5-T to 3-T MRI is a current trend for PC diagnosis. Thus, we selected a 3-T MRI protocol for homogeneity and future applicability. Someone can raise an issue of selection bias. However, multiparametric prostate MRI has been a routine evaluation before RP. And the selection between 1.5-T and 3-T was determined just by schedule of the test. Thus, allocation was almost random assignment, although it was not intended. Of 237 patients met AS candidate eligibility, 116 and 117 men underwent 1.5-T and 3-T multiparametric prostate MRI, respectively in the present study. Four patients did not take prostate MRI in our institution because they underwent it before referral to our hospital. We graded ADC using the Likert scale rather than b-value criteria. The ADC Likert scale may be subjective, but it is widely applicable in daily practice. Our findings also indicated that ADC grade could help to select patients suitable for AS. Particularly, we focused on excluding inappropriate men who harbored unfavorable pathological features.

We defined unfavorable pathological features as nonorgan confined disease or pathological Gleason score ≥ 7 (4+3) to identify men who should definitely be excluded. The PIVOT trial demonstrated no definitive survival benefit of RP compared to observation for men with localized PC [6]. RP was associated with survival benefit among men with PSA > 10 ng/mL and possibly among those with intermediate- or high-risk tumor. Furthermore, recent data from AS series showed generally good performance [2,7]. Gleason score 7 (4+3) clearly differs from Gleason score 7 (3+4) and is similar to Gleason score 8 with respect to recurrence and PC-specific survival [22,23]. In our cohort, one patient had Gleason score ≥ 8. Although many AS trials use biopsy Gleason grade 4 patterns as a trigger for definitive treatment, many Gleason 7 (3+4) cases are upgraded in RP specimens [24]. Thus, pathological Gleason score ≥ 7 (4+3) is a reasonable criterion for unfavorable features in RP specimens.

Our cohort was selected using current AS eligibility criteria, and no patients demonstrated extremely unfavorable pathology, such as seminal vesicle invasion or lymph node metastasis. However, 9 (7.7%) experienced extraprostatic extension, and 71 (60.7%) had pathological Gleason score ≥ 7. When our definition of unfavorable pathological features was applied, 12 men (10.3%) were classified as unsuitable for AS. ADC grade was useful to exclude these unsuitable patients for AS. Its OR was more than 10 and better than preoperative biopsy parameters both in univariate and multivariate analysis. Although positive predictive value was low, negative predictive value was very high. Thus, when ADC grade is low (e.g., ≤ 3), patients can comfortably undergo an AS protocol. Furthermore, we observed no cases of insignificant cancer among ADC grade-5 patients, and no unfavorable pathology was detected in ADC grade-1 patients. ADC grade markedly added value to conventional clinical information for selecting AS candidates, with an improvement in AUC of 0.130 (0.861 vs. 0.731) (Table 3). By bearing in mind these characteristics, we can select AS patients with prudence.

In the present study, the rate of upgrading to pathological Gleason score ≥ 7 (60.7%) seems to be higher than other data. This Gleason upgrading in contemporary RP series is about 35% [25], however it is higher in the patients who underwent RP following initial AS up to 55.2% [26]. We consider higher upgrading rate in the present study may be caused by the aggressive phenotype of PC in Korean population than in Western series [27,28]. Gleason score upgrading in surveillance candidate who actually underwent RP ranged from 41.6% to 50.6% in other Korean cohort [29].

Although the results of this study are clinically significant, it also has several limitations. It was a single-center, retrospective analysis. Thus someone may claim selection bias. However, AS was not a standard treatment in our institution and almost all of the very low-risk PC patients were undergone RP. Furthermore, almost all patients underwent prostate MRI, and selection of magnetic field strength was determined not by clinical parameters but by schedule of the test. Thus we consider that selection bias in the study is not significant. All MRI were taken after biopsy, thus it could be considerable limitation, even though ADC is not much affected by hemorrhage. As another limitation, we did not test using various AS criteria. However, the clinical contexts of the various criteria were similar. Our results warrant further multicenter large-scale investigation or prospective study. In the long term, after ADC grade is incorporated into AS criteria, we should confirm how much percentage of AS-eligible patients who undergo definitive treatment will be decreased.

In summary, ADC grade determined with 3-T DW-MRI is useful for predicting AS candidates with unfavorable pathological features. This result should be confirmed by large-scale multicenter studies or prospective clinical trials. Our finding suggests that incorporating ADC grade as a criterion for selecting candidates for AS among PC patients.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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